Remarks

Claims 1-24 are pending. Claims 3, 20, and 24 have been canceled without prejudice. Applicants have amended claims 1, 2, 4-19, and 21 to facilitate prosecution but maintain that the specification enables the production of transgenic, non-human mammals. Support for the amendments can be found at least in the claims as filed.

Applicants have provided a new Declaration, which they believe to be in compliance with 37 C.F.R. § 1.67(a). The post office address has been supplied for each inventor. Applicants believe this moots the Examiner's objection.

A. Introduction

The claimed technology is directed to transgenic, non-human mammals comprising erythrocytes that produce a human hemoglobin, but fail to produce adult hemoglobin endogenous to said non-human mammal. The claimed animals survive on human hemoglobin alone. Many of the techniques needed to make and use these transgenic animals were present in the art for years before Applicants' application, but those skilled in the art lacked the motivation and expectation of success that a non-human mammal could live on human hemoglobin alone.

Methods and materials for making transgenic mice and knockout mice existed for years before the filing of the present application. The contribution of the Applicants, in part, arises from the fact that prior to the present application no mammal, other than human of course, survived on human hemoglobin alone. As is discussed below, those of skill in the art, did not expect that any mammal other human, mouse or otherwise, would be able to survive in such a way. The oxygen affinities of cross species hemoglobin, the homologies of hemoglobin, and the very precise requirements needed for overall oxygen delivery systems indicated that the mouse reduced to practice in the present application would not have a reasonable expectation of survival.

B. Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-24 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled for "a transgenic non-human mammal comprising erythrocytes that produce a human hemoglobin, but fail to produce adult hemoglobin endogenous to said nonhuman mammal."

First, applicants appreciate the acknowledgment by the Examiner that the specification is enabled for a "transgenic mouse whose genome comprises a human LCR γ-β hemoglobin

switching DNA construct, wherein said genome is further homozygous for murine α- and β-globin knockout alleles such that said knockout alleles result in said mouse failing to synthesize murine hemoglobin, and wherein said hemoglobin switching construct is expressed such [that] said mouse develops hemolytic anemia." The Applicants have amended the claims to recite "transgenic mouse" rather than "transgenic non-human mammal" to facilitate prosecution. Applicants believe the claims are enabled for their full scope and reserve the right to prosecute these claims in a continuation application.

Thus, the Applicants understand the remaining area of difference between the PTO and the applicant, with respect to enablement, is that switching construct technology is allegedly required to enable the claimed subject matter. The PTO indicates that the disclosed compositions require a DNA switch construct. This is generally incorrect. A switch construct is not needed for transgenes, but is helpful for transgenes related to sickle cell hemoglobin. As is discussed in the application at page 25, lines 5-14, the switch construct is used to offset the effect of the transgenic sickle hemoglobin in the early developmental stages of the mouse, when reduced oxygen capacity may not be tolerated like it is an adult. As explained by Dr. Townes, the switching construct is not needed in most constructs, because for example, fetal development is unaffected by reliance on only β-globin for example, rather than fetal γ-globin at the early stages of development. (Townes Declaration). Dr. Townes states, "Switching constructs are not required for all hemoglobin transgenes. We used a construct that switches from human gamma (fetal) to human beta (adult) globin during development when producing our mouse model of sickle cell disease. In this case, the production of human fetal hemoglobin is important to inhibit red cell sickling during fetal development and in new born animals. When a normal adult beta globin gene is linked to the LCR, normal adult hemoglobin is synthesized in the fetus and newborn and these animals are normal." (Townes Declaration). Thus, contrary to the position of the PTO, the claims are not too broad relative to the switching construct because a switching construct is not needed for operability of the full breadth of the claim.

C. Rejection Under 35 U.S.C. § 103

Claims 1-19 are rejected under 35 U.S.C. § 103 for allegedly being unpatentable over Paszty et al., "Lethal α-thalassaemia created by gene targeting in mice and its genetic rescue," Nat Genet., 11(1):33-9 (1995) ("Paszty"), and Ciavatta et al. "Mouse model of human β^0 thalassemia:

targeted deletion of the mouse β^{maj} - and β^{min}-globin genes in embryonic stem cells," Proc. Natl. Aced. Sci. USA 92:9259-9263 (1995) ("Ciavatta") taken with Rubin et al., "Hypoxia-induced in vivo sickling of transgenic mouse red cells," J. Clin. Invest., 87:639-47 (1991) ("Rubin"), and Fabry et al. "A second generation transgenic mouse model expressing both hemoglobin S (HbS) and HbS-Antilles results in increased phenotypic severity," Blood, 86:2419-28 (1995) ("Fabry").

Claims 21-24 are rejected under 35 U.S.C. § 103 for allegedly being unpatentable over Paszty and Ciavatta taken with Rubin and Fabry in further view of Westphal, "Tansgenic mammals and biotechnology," FASEB J., 3(2):117-20 (1989) ("Westphal").

Claims 1-19 are not obvious over Pastzy and Ciavatta in view of Rubin and Fabry. The standard for obviousness requires both a motivation to arrive at the claimed subject matter as well as a reasonable expectation of success that the claimed subject matter would work. A motivation to try is not sufficient. A prima facie case of obviousness has not been provided because no motivation in any of the cited references, or in the art as a whole, has been provided. Furthermore, even if there was a motivation to make the claimed animals, those of skill in the art would not have had a reasonable expectation of success that the claimed mammals would live. Even if one assumes that there would have been motivation to make the claimed animals by mating the mice of Ciavatta and Paszty together, there is no reasonable expectation that these mice would live. In fact, as indicated by Dr. Townes, it was thought that mice would be unable to live on non-native hemoglobin alone. Dr. Townes states, "The production of mice that survive on human hemoglobin is predictive of the survival of larger mammals. The physiology of the mouse is more different from humans than is the physiology of the cow or sheep and humans. The high metabolic rate of the mouse requires efficient oxygen delivery and the oxygen affinity of mouse and humans are significantly different. Therefore, we could not predict that the mouse would survive on human hemoglobin. However, the fact that mice did survive exclusively on human hemoglobin makes it likely that large animals would also survive solely on human hemoglobin." (Townes Declaration).

Applicants also note the Office Action has set out many factors that would have made the invention non-obvious. In this regard, the Office Action states, "in view of the . . . underdeveloped state of the ES cell art for species of mammals other than mice, the unpredictable state of the art with respect to the generation of transgenic non-human mammals of all species

expressing identical levels of a transgene and developing identical phenotypes due to such expression . . . it would have required undue experimentation of one skilled in the art to make and/or use the claimed invention as broadly claimed with a reasonable expectation of success." Office Action at page 8, line 2. Therefore, Applicants respectfully traverse this rejection.

D. Rejection Under 35 U.S.C. § 102

Claim 20 was rejected under 35 U.S.C. § 102(b) as being anticipated by Dong et al. Dong et al. teaches the purification of human hemoglobin. Claim 20 was also rejected under 35 U.S.C. § 102(a) as being anticipated by U.S. Patent No. 5,877,288, which teaches anti-sickling human hemoglobin. Claim 20 was further rejected under 35 U.S.C. § 102(f) as allegedly not invented by the Applicants. As claim 20 is cancelled without prejudice as Applicants reserve the right to prosecute this subject matter at a later date as Applicants believe the subject matter patentable, and these rejections are moot.

E. Double Patenting Rejection

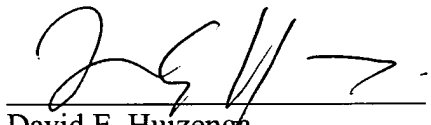
Claim 20 was rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 5,877,288. As claim 20 is cancelled without prejudice, these rejections are moot.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $60.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(1), and a Request for a One (1) Month Extension of Time are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



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